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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,745	06/24/1998	SUDHIR AGRAWAL	475.08.642CI	3401

7590 07/01/2004

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/103,745	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	J. Douglas Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/8/2004
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed April 8, 2004 has been considered. Rejections and/or objections not reiterated from the previous office action mailed are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 8, 2004 has been entered.

Response to Arguments, Double Patenting

Claims 1, 3 and 4 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,856,462 for the same reasons of record cited in the Office action mailed September 9, 1999. It is acknowledged that Applicant's response to the double patenting rejection of Sept. 9, 1999 indicated that, should

any pending claims be indicated as allowable, applicant will file a Terminal Disclaimer disclaiming the portion of the term of the patent beyond the expiration date of U.S. Patent Number 5,856,462.

Response to Arguments, Claim Rejections - 35 USC § 112

Claims 3 and 4, stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using the claimed compounds in cell culture, or to reduce some measures of immune stimulation, does not reasonably provide enablement for methods of treating mammals or methods of therapy using the instantly contemplated compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the Office action of September 9, 1999.

Applicants traverse the instant rejection by asserting that evidence has been provided in the form of publications indicating that exemplary oligonucleotides taught by the specification cause a beneficial antisense-mediated inhibition of target gene expression *in vivo*. Applicants also allege to have supplied further evidence that the claimed scope is commensurate with the teachings of the specification.

Agrawal (applicants' exhibit A) is alleged to demonstrate that substitution of 2'-O-methylribonucleosides for CpG deoxyribonucleosides minimizes immune stimulation and asserts that the activity of antisense-mediated antitumor effects of the modified CpG oligo is retained. Applicants point out that the antisense oligonucleotides used in this study were directed against

the Rl α subunit of protein kinase A (PKA), and have been shown to both down-regulate RI α subunit expression and inhibit the growth of a human colon cancer tumor in nude mice.

In response, it is noted that the results as described by applicants are considered to support claims to inhibit the expression of the RI α subunit of PKA from human colon cancer tumor in nude mice. However, applicants' claims are much broader than this, encompassing inhibiting RNA target, in any disease related to aberrant gene expression in any mammal. This disclosure is simply not considered to support such breadth. Furthermore, such data related to inhibition of PKA is noted as "not shown" (page 138, last sentence of conclusion), thus preventing any evaluation of such data. It is noted that the present inventors are also the authors of this paper; the opportunity to provide said data exists in the form of a declaration under 37 CFR § 1.132,; such provision may be considered supportive of applicants claimed methods of inhibiting gene expression in the whole animal.

Applicants have addressed the issue of the breadth of the claims in relation to the teachings of the specification, and conclude that the specification indeed supports the claimed breadth. Applicants do this by *inter alia* arguing that they are not required to conform to FDA standards to be enabled for patentability.

Such a requirement has never been placed on applicants at any point in prosecution history, nor is one now being made. The reference to FDA trials was first made by applicants, who argued that there are numerous antisense compounds now being tested in clinical trials, to which it was responded that most of those trials have been unsuccessfully concluded, as evidenced by a Reuter's news service citation that "Isis currently makes the world's only commercial antisense drug -- a treatment for a rare type of eye infection in AIDS patients. Many

once-promising antisense drugs have failed, including experimental therapies from Isis for HIV and genital warts." Thus, any reference to FDA clinical trials was first set forth by applicants, and was responded to with a statement of fact regarding the state of the art of the therapeutic use of antisense oligos *in vivo*.

Applicants have also argued that references submitted by applicants support the notion that screening *in vitro* for antisense inhibition can be correlated with *in vivo* success. Specifically applicants state that the reference of Milner is exemplary of "many methods available for rapid and efficacious screening of possible oligo sequences for a given target." Applicants also provide other references which are published well after applicants filing date, which is the time at which enablement must be present (see M.P.E.P. 2164). Applicants allege that these references indicate that "scanning-array technology [has] shown a good correlation between the hybridization of an ASO (antisense oligonucleotide) to a synthetic RNA and the ability of that ASO to direct RNase H cleavage of the pre-mRNA, both in vitro and in vivo" (Dickson *et al.*), and that another study shows that antisense oligonucleotides directed against cyclin mRNA, which were selected by hybridization to scanning arrays in vitro, are effective in *in vivo* in Xenopus oocytes (Sohail *et al.*). Other publications in which candidate antisense oligonucleotides are screened for their effectiveness in an in *in vivo* (animal) model using only routine skill in the art further demonstrate the enablement of the claimed invention. (Szyf *et al.*, 2002) and Gleave *et al.*, 2001).

Milner et al. does teach a high throughput screening process as cited by applicant, performed *in vitro*. While applicants statements that the methods of Milner assist one of skill in circumventing the widely recognized problem of identifying target sites, the structure of RNA *in*

vivo differs unpredictably from the structure of the same RNA *in vitro*, because as one of skill in the art is aware, the expression of a RNA transcript is tissue specific, thus retaining different translational cofactors depending on which tissue its in, which in turn contributes to unpredictable changes in RNA secondary structure. Thus, while Milner may assist in using *in vitro* screening results to determine accessible sites *in vitro*, it is maintained that conversion of these results into successful predictions of what will occur *in vivo* is by no means routine and requires undue experimentation.

Moreover, the statement of Dickson *et al.* is considered to be taken out of its context, because the premRNA referred to as cleaved is only one transcript, and its application to other transcripts is at best uncertain, and further because the statement itself is supported only by a reference to another journal article, making its independent evaluation impossible from the mere statement of Dickson.

Applicants reference of Sohail, citing the effectiveness of screening methods for predicting gene inhibition in Xenopus oocytes (i.e. frog eggs), which applicants cite as being performed "*in vivo*" is actually performed outside the whole animal, and is thus not considered relevant to the instant claims, which specifically recite inhibition of gene expression in mammals. The argument that Sohail defines *in vivo* as having to do with a living cell, while most others define *in vivo* as in the whole animal is considered to be a semantic argument without a difference, particularly when the claim language and the instant rejection are clear that the claimed methods are to be practiced in the whole animal.

Szyf does not appear to disclose any data relating to the administration of antisense oligos to whole animals, and applicants have not pointed to any specific teaching from the reference, so

what level of support this reference provides for applicants arguments is unclear. Gleave *et al.*, published 4 years after applicants effective filing date, does indicate success *in vivo* using an antisense tested *in vitro*, such results are only obtained after injecting the same cells tested *in vitro* into a mouse that has its immune system effectively abolished, thus not considered to significantly parallel and is not considered to be particularly representative to the treatment of disease as claimed instantly. While occasional success has been noted using antisense *in vivo*, such success is not considered to be predictable based on the results of tests performed *in vitro* as cited and documented in the previous action, thus requiring one of skill to engage in undue trial and error experimentation to practice the instant invention.

Applicants argue that the previous Office action fails to specifically characterize Applicants' contribution to the art and thereby unduly leads to an overdrawn burden upon the Applicants to show enablement. Applicants argue they are not claiming every method utilizing antisense to treat disease, but rather methods using particular types of modified CpG containing phosphorothioate oligonucleotides that have reduced undesirable side effects. To require that Applicants demonstrate efficacious treatment of all diseases associated with aberrant gene expression is undue because Applicants are specifically claiming only the improved methods that utilize the modified CpG oligonucleotides taught.

In response it is set forth that no requirement has ever been placed upon applicants to demonstrate treatment of all diseases. It is agreed that the enablement requirements do not require that every embodiment be operable. However, it is a fact that the claim language does include within its scope *any* disease caused by gene aberrant expression. In contrast to the claimed coverage, neither the specification nor the prior art has shown any treatments of any

disease. This gap between what is claimed and what is available to the skilled artisan via the teachings of the specification and the prior art simply cannot be covered by prophetic teachings of the specification and the lack of support from the prior art to predict whether gene inhibition *in vivo* will occur and any disease so treated.

Applicants have asserted that many patents have been granted to compositions and methods for treating various diseases using antisense oligonucleotides directed against specific sequences. Applicants argue that it is therefore clear that there are many oligonucleotides that have been recognized to meet the standards of patentability for being useful in modulating gene expression. However, each patent is evaluated based on the record for that patent, and is evaluated based on a case by case approach. Thus, while claims may have been issued that cover *in vivo* whole animal gene inhibition, it is not the claims *per se* that are considered supportive of applicants assertions of enablement, but rather what the patents teach that may or may not be so supportive. Applicants are invited to indicate what specifically about these patents is considered supportive to applicants instant claims; however, in the absence of any such indications, a review of these patents indicates nothing that is considered to augment applicants disclosure in a way that overcomes the instant enablement rejection. The rejection is thus maintained.

Response to Arguments, Claim Rejections - 35 USC § 102

Claim 1 stands rejected under 35 U.S.C. 102(a) as being anticipated by either of Krieg et al. (WO/9602555A1) or Krieg et al. (Antisense or Nucleic Acid Drug Development, of record), for the same reasons of record as set forth in the Office action of September 9, 1999.

Applicants have amended the claim language to delete references to "inverted CpG", which were taught by both Krieg references. The rejection had been maintained because the specification taught that an inverted CpG is simply a GpC, and because GpC's are present in the sequences of Krieg. Applicants assert that the instant amendment obviates the instant rejection, and suggests that the remaining limitations drawn to alkylphosphonate- modified CpGs, 2'-O-substituted CpGs, stereospecific phosphorothioate CpGs, phosphotriester CpGs, phosphornmidate CpGs, and 2'-5' CpG's.

However, the rejection is maintained because the reference of Krieg continues to teach some of the remaining limitations, particularly in view of the broad definitions provided for the limitations in the specification. For example, the specification defines a stereospecific phosphorothioate CpG as a CPG dinucleoside in which the C nucleoside and the G nucleoside are covalently linked to each other through a stereospecific phosphorothioate internucleoside linkage. It is argued that any phosphorothioate linkage is stereospecific. Although Krieg *et al.* does not describe in which manner they are stereospecific, the instant definition of the specification does not require any particular stereospecificity; by nature of their very existence, the phosphorothioate containing CpGs are stereospecific in some manner.

Furthermore, both Krieg papers teach alkylphosphonate modified oligos (for example at page 20 lines 20-30 of '555, or materials and methods of Krieg Antisense and nucleic acid and development. For these reasons, both Krieg papers are considered to teach all the elements of applicants' claim.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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